Effects of the Somatostatin Analogue, Octreotide, in Polycystic Ovary Syndrome

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In view of the association of hyperinsulinemia with elevated luteinizing hormone (LH) levels and hyperandrogenism in polycystic ovary syndrome (PCOS), the effect of octreotide was investigated in women with PCOS. Twelve amenorrheic women were treated with 100 μg octreotide twice a day for 7 days; 13 infertile women unresponsive to clomiphene citrate were treated either with octreotide (100 μg twice a day from day 1 of the menstrual cycle until corpus luteum formation) in addition to human menopausal gonadotropins (HMG) or with HMG alone. Octreotide significantly reduced the 4-hour integrated LH concentrations. LH pulse amplitude and nadir concentrations, and LH, testosterone, androstenedione, and estradiol responses to a gonadotropin-releasing hormone (GnRH) analogue in amenorrheic PCOS women. Octreotide treatment also resulted in a more "appropriate" hormonal milieu at the time of human chorionic gonadotropin (HCG) injection in the infertile women, with LH and testosterone levels being reduced while follicle-stimulating hormone (FSH) levels increased. Orderly follicular growth occurred, with one or two mature follicles being present at the time of HCG injection in cycles in which octreotide was given together with HMG. There were no cases of hyperstimulation, even in women who had previously hyperstimulated after HMG alone. Octreotide thus inhibits LH and androgen secretion and may improve ovulatory performance in infertile women with PCOS.

POLYCYSTIC OVARIAN syndrome (PCOS) is the most common cause of menstrual disturbance and infertility in women attending endocrine clinics. The syndrome is characterized by increased luteinizing hormone (LH) concentrations and increased ovarian androgen production.[1] The increased LH levels are thought to be the critical factor in both the infertility and increased early pregnancy loss[2] and in the increased incidence of hyperstimulation after human menopausal gonadotropin (HMG) treatment in women with PCOS. Nevertheless, pretreatment with gonadotropin-releasing hormone (GnRH) agonists, which decrease LH levels, had no significant effect on either subsequent fertility, the miscarriage rate, or the incidence of hyperstimulation.[3,4]

However, hyperinsulinemia is also associated with the increased androgen and LH levels in PCOS,[5-8] and it has been suggested that hyperinsulinism could contribute, at least in part, to the high LH amplitude and gonadotrophin sensitivity to GnRH observed in women with PCOS.[9]

We therefore investigated the short-term effect of the long-acting somatostatin analogue, octreotide, in women with PCOS and found the analogue suppressed hyperinsulinemia and LH and ovarian androgen secretion.[10] These findings raised the possibility that octreotide might have a therapeutic application in infertile women with PCOS.

The present study was undertaken (1) to amplify our preliminary observations of the effect of octreotide on endocrine parameters in PCOS (part A), and (2) to assess the influence of octreotide on ovulatory performance in infertile women with PCOS undergoing treatment with HMG (part B).

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PATIENTS AND STUDY DESIGN

Part A

The subjects were 12 consecutive, hirsute, amenorrheic women with PCOS, aged between 17 and 33 years. Eight women were overweight (body mass index [BMI] > 25). Elevated LH concentrations with basal levels between 10 and 20 mU/L, elevated testosterone and/or androstenedione blood levels, decreased serum hormone binding globulin (SHBG) concentrations, and the typical ultrasound picture of PCOS—peripheral cysts and follicles less than 5 mm in diameter, and a highly echodense stroma[11]—were present in each case. The study was approved by the local (Belgrade) hospital ethics committee, and each woman gave informed consent to participate in the study.

The investigation protocol was as detailed previously; in summary, LH pulsatility, androgen concentrations, and hormonal responses to an oral glucose load and to administration of a GnRH agonist (buserelin) were measured before and after 7 days' treatment with octreotide 100 μg twice a day.[10]

Part B

Thirteen consecutive, hirsute, infertile women with PCOS unresponsive to clomiphene citrate (aged between 24 and 38 years; mean BMI, 26.8 ± 6.4) were randomized initially to receive either HMG treatment alone or HMG and simultaneous daily octreotide. Women starting on HMG alone were switched to combination treatment (HMG + octreotide) after two cycles of HMG alone. Treatment with HMG + octreotide was then continued for a maximum of six cycles, unless they conceived. Seven women were treated with HMG alone initially (three of them switched to HMG + octreotide in subsequent cycles), and six women were treated with HMG + octreotide from the beginning of the trial.

All patients had classic features of PCOS on pelvic ultrasound. Women were only considered for HMG or HMG + octreotide therapy after failure to conceive with clomiphene citrate given successively in doses up to 200 mg daily.

Treatment regimen

Octreotide was self-administered subcutaneously (SC) in a dose of 100 μg twice a day. The injections were started on day 1 of each

Table 1. Effects of 7 Days of Octreotide (100 μg twice a day) on LH Release in 12 Amenorrheic Women With PCOS

	Before	After	*P* Value
Integrated concentration (mU/L)	13.9 ± 1.7	9.7 ± 1.3	<.005
Mean peak amplitude (mU/L)	17.1 ± 2.5	11.8 ± 6.3	<.005
Mean nadir concentration (mU/L)	11.1 ± 1.6	7.7 ± 1.3	<.005
Mean response to buserelin*	1,225.0 ± 92.3	685.5 ± 82.5	<.005

NOTE. Results are means ± SE.
* Expressed as AUC.

menstrual cycle and continued until 7 days after the human chorionic gonadotropin (HCG) injection. Octreotide therapy was resumed on day 1 of the next menstrual cycle.

HMG was administered according to a "1, 3, 5" regimen, as in our previous studies,[12,13] with the initial HMG injection being given between days 3 and 5 of the cycle. The starting dose was 4 ampoules HMG, each containing 75 IU, and it was increased by one ampoule per injection in successive cycles.

Ultrasound scans (USS) were performed initially between days 3 and 5, before the start of HMG therapy, and then after 7 days of treatment to assess follicular development and endometrial thickness. If a mature follicle (diameter 18 mm or more) was present, the ovulating dose of HCG (5,000 U, or less if more than one follicle was present) was given, but if follicular development was inadequate, additional HMG was given and USS were repeated daily until at least one mature follicle was seen. USS were repeated in the luteal phase (7 days after HCG injection).

Serum LH, follicle-stimulating hormone (FSH), testosterone, estradiol, progesterone, prolactin, and SHBG concentrations were measured on day 1 (the day of the first HMG injection) of all treatment cycles, on day 8, and then daily if the ovarian USS response was inadequate until HCG had been injected. Blood samples were also taken for hormone measurements in the luteal phase, 7 days after HCG injection.

Hormone Assays

Serum LH and FSH concentrations were analyzed by double-antibody radioimmunoassay using a kit from Pharmacia (Uppsala, Sweden). Serum testosterone and estradiol levels were determined by Serono-Biodata commercial kits. The assays of androstenedione and dehydroepiandrosterone were performed with Diagnostic Product kits. Serum SHBG levels were determined with the Biodata commercial kit, which is based on the method for indirect determination of SHBG through the evaluation of dihydrotestosterone binding capacity. Serum insulin and C-peptide concentrations were determined by Byk-Mallinckrodt kits. All samples from control and posttreatment tests for each individual subject were assessed together to avoid interassay variations. Integrated serum LH concentrations and quantitative analyses of LH secretion were performed as in the previous study.[10]

Statistical Analysis

All results are reported as the mean ± SEM. Summary measures[14] were applied to the analysis of serial measurements. Hormone responses after buserelin or an oral glucose load were assessed in relation to the area under the curve (AUC). Statistical significance was calculated by nonparametric methods using either the Wilcoxon signed-rank test for paired observations or the Mann-Whitney *U* test, as appropriate. Linear regression and Kendall's rank were applied for analyzing correlations between parameters.

RESULTS

Part A

Octreotide treatment induced a significant decrease in mean peak LH pulse amplitude, average nadir concentrations, and integrated concentrations over 4 hours (Table 1). There was a significant ($r = .765$, $P = .01$) positive correlation between LH peaks and nadir concentrations before and during octreotide treatment. However, no significant changes were observed in the number of LH pulses over 4 hours. Similarly, there was no change in FSH pulsatility after octreotide treatment.

LH release after a single SC injection of 40 μg buserelin (expressed as AUC) was significantly lower after 7 days of octreotide treatment (Table 1). Although some decrease in the FSH response to buserelin was also observed after 7 days of octreotide, the differences were not significant.

Mean estradiol levels over 4 hours were significantly lower after octreotide (Fig 1), as were estradiol responses after a single SC buserelin injection (AUC, 4.45 ± 0.38 before and 2.73 ± 0.40 during octreotide; $P < .02$).

Mean testosterone levels over 4 hours decreased significantly with octreotide treatment (Fig 1), as did the mean level observed during the 10 hours after buserelin injection (AUC, 56.12 ± 12.69 before and 40.10 ± 9.48 during octreotide; $P < .02$).

Mean androstenedione levels over 4 hours also decreased significantly with octreotide treatment (Fig 1), as did the mean levels observed during the 10 hours after buserelin (AUC,

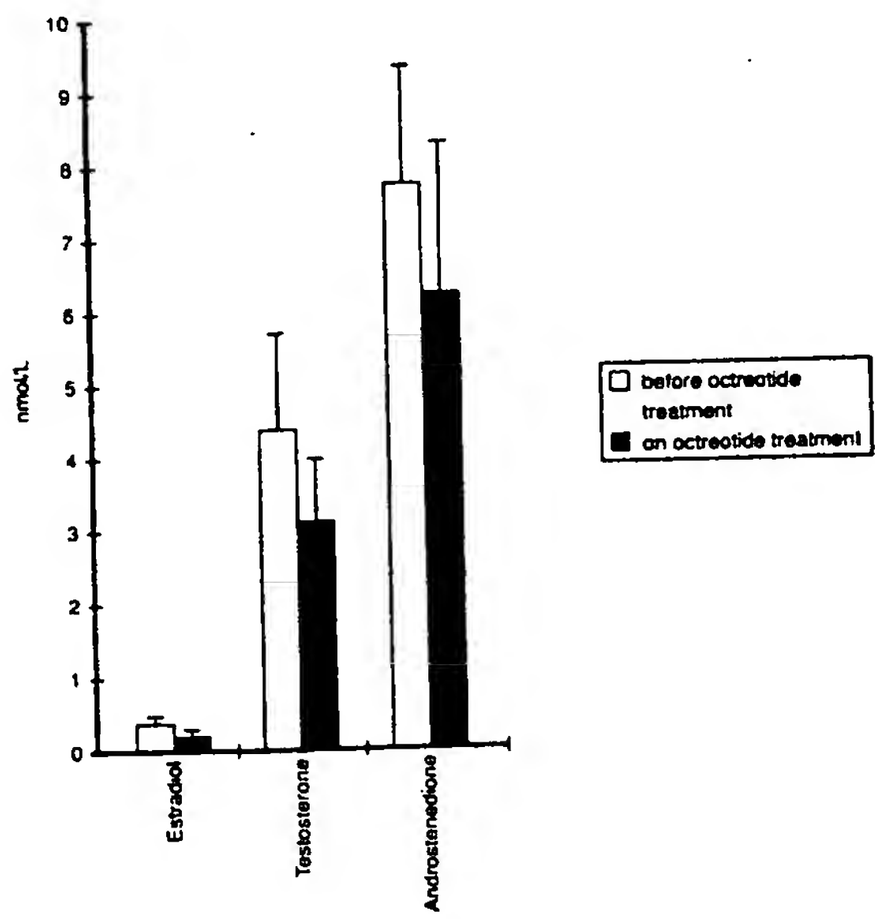

Fig 1. Effects of 7 days of octreotide treatment (100 μg twice a day) on mean estradiol, testosterone, and androstenedione levels over 4 hours in 12 amenorrheic women with PCOS (mean ± SE) before (□) and during (■) octreotide treatment (*$P = .005$, **$P = .01$, ***$P = .02$).

Table 2. Results of Induction of Ovulation in Women With PCOS

	Treatment Regimen	
	HMG	HGM + Octreotide
Patients	7	9
Treatment cycles	12	21
Overstimulation	6 (50%)	0
Omitted cycles due to persistent follicle	4 (33.3%)	4 (19.0%)
Ovulations	6 (50%)	8 (38%)
Pregnancies	0	2
Mean amplitude of HMG per cycle	21.7 ± 2.4	21.7 ± 1.9
Mean duration of therapy until day of HCG	14.3 ± 0.8	13.1 ± 0.5

89.68 ± 23.85 before and 66.48 ± 19.82 during octreotide; $P < .03$).

Before octreotide, glucose tolerance was normal in all 12 women. However, after seven days of octreotide treatment, six women developed glucose intolerance, with a peak glucose concentration greater than 10.00 mmol/L. The blood glucose AUC was significantly higher during octreotide than before (46.88 ± 3.65 *v* 35.84 ± 1.92, $P < .02$). Although there were no significant differences between fasting insulin and C-peptide concentrations before and during octreotide treatment, the responses during the oral glucose tolerance test were significantly lower with octreotide treatment ($P < .002$ and $P < .001$, respectively).

Part B

The results of induction of ovulation with HMG or HMG + octreotide are summarized in Table 2 and Fig 2. Orderly follicular growth occurred in the majority of cycles in which octreotide was given together with HMG, with the result that one or, at most, two mature follicles were present at the time of HCG injection. This contrasts with the far greater, sometimes "explosive," follicular development characteristic of HMG injection alone. The mean number of follicles larger than 15 mm in diameter on the day of HCG was significantly higher in cycles in which HMG alone had been administered than in those in which octreotide was given together with HMG (4.5 ± 0.6 *v* 2.4 ± 0.3, $P = .0017$). However, there was no difference in the mean number of HMG ampoules per cycle between those treated with HMG alone and those receiving octreotide + HMG (Table 2).

Treatment had to be interrupted due to a persistent follicle at the start of the cycle in four cycles in both the HMG alone (33.33%) and HMG + octreotide–treated groups (19.04%).

Multiple follicular development occurred in only three of the HMG + octreotide–treated cycles. Although mild ovarian enlargement was evident on ultrasound 7 days after HCG injection in three cycles, none of these cases showed clinical features of hyperstimulation. In fact, even in the three women who had previously experienced severe abdominal pain with ovarian enlargement and multiple cystic formation during HMG therapy alone, there was neither symptomatic nor ultrasound evidence of hyperstimulation when HMG was given together with octreotide. By contrast, hyperstimulation occurred in six of 12 cycles in which HMG was given alone, and HCG had to be withheld on three occasions because of the degree of hyperstimulation.

All women receiving octreotide complained of diarrhea (loose motions approximately three times a day), and one woman discontinued therapy because of this.

To date, two women have conceived—one in her first HMG + octreotide cycle, who unfortunately miscarried at 7 weeks gestation; the other conceived in her third cycle of combined therapy.

Progesterone concentration in the luteal phase (ie, 7 days after the ovulating dose of HCG injection) was 38 nmol/L or higher in six of 12 HMG cycles and in eight of 21 HMG + octreotide cycles (Table 2).

LH levels were significantly lower, both in the follicular phase and on the day of HCG administration, in cycles in which HMG + octreotide was given than in cycles when HMG was given alone (Fig 2, Table 3). Also, in the early follicular phase, a more "appropriate" hormonal milieu (lower LH, higher FSH, lower testosterone levels) was observed with combined treatment than with the pretreatment cycle in the same women (Table 3).

DISCUSSION

Octreotide thus induces a significant decrease both in LH pulse amplitude and in the LH response to buserelin in women with PCOS. Since LH pulse frequency is unchanged, it is likely that octreotide achieves this effect as a result of an influence exerted at the pituitary level.[15]

Although octreotide seems to act directly at the pituitary level, probably by decreasing the sensitivity of gonadotrophs to unaltered GnRH pulses, the analogue could also influence

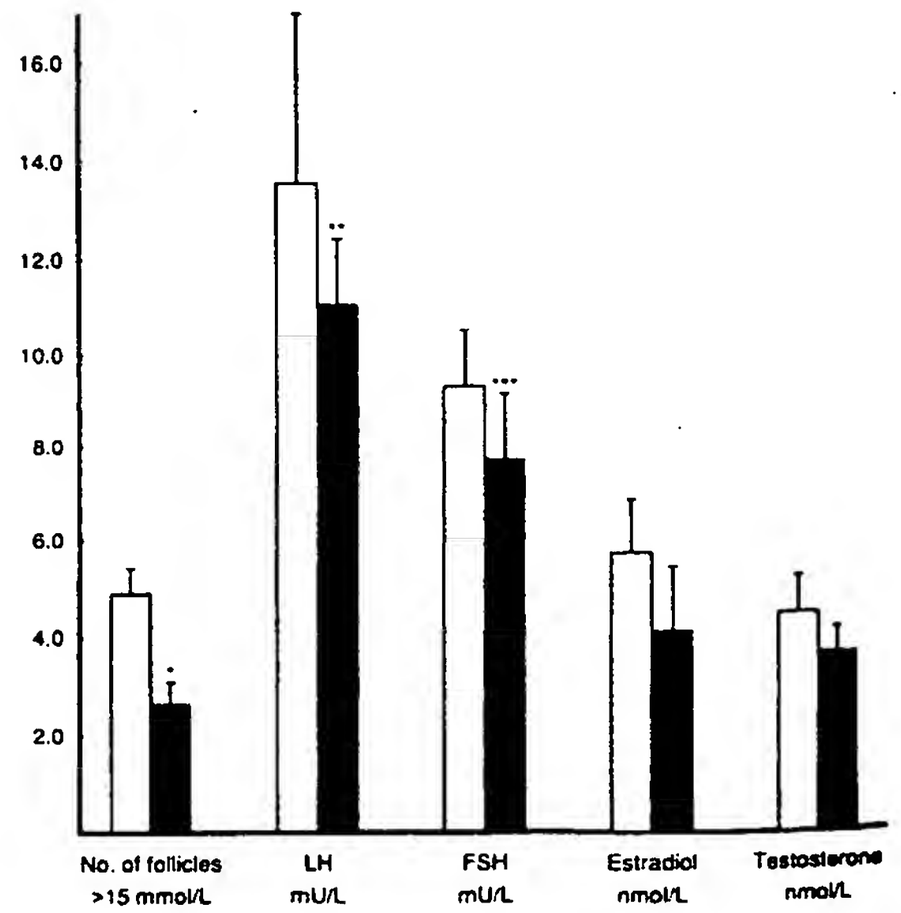

Fig 2. Hormonal and follicular characteristics (mean ± SE) on the day of HCG administration in women with PCOS treated with HMG alone (□) or HMG + octreotide (■). (*$P = .0017$, **$P = .042$, ***$P = .031$).

Table 3. Hormonal Characteristics of Women With PCOS in the Early Follicular Phase (Days 3 to 5) Treated With Either HMG or HMG + Octreotide

	Pretreatment Cycle		Treatment Cycle§	
	HMG	HMG + Octreotide	HMG	HMG + Octreotide
LH (mU/L)	12.92 ± 2.57	11.53 ± 2.33	13.39 ± 3.12	8.59 ± 1.29*
FSH (mU/L)	6.28 ± 0.62	4.62 ± 0.53‡	7.21 ± 0.56	5.14 ± 0.38†
Estradiol (pmol/L)	190.00 ± 22.78	208.89 ± 31.24	169.50 ± 14.68	178.67 ± 16.67
Testosterone (nmol/L)	2.73 ± 0.16	3.17 ± 0.40	2.36 ± 0.14	2.78 ± 0.16

NOTE. Results are means ± SE.

* $P = .023$, † $P = .0035$, ‡ $P = .035$: HMG group versus HMG + octreotide group.

§ Before the start of HMG injection.

LH secretion indirectly as a result of the lower insulin levels, that in turn decrease sensitivity of the gonadotrophs. The results of the present study therefore imply that the inhibition of ovarian steroidogenesis is secondary to the inhibition of LH secretion induced by octreotide.

Octreotide treatment seems to result in a more appropriate hormonal milieu at the time of HCG injection. Thus, LH and testosterone levels are reduced while FSH concentration is increased after octreotide. Furthermore, orderly follicular growth was apparent in cycles in which octreotide was given together with HMG, and there were one or, at most, two mature follicles at the time of HCG injection. The fact that there were no cases of hyperstimulation when octreotide was given together with HMG, even in women who had previously been hyperstimulated with HMG alone, gives preliminary evidence that octreotide could be a therapeutic adjunct during gonadotropin-stimulating therapy for infertile women with PCOS.

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